



Procalcitonin Uptake and Effect on Antibiotics Stewardship: A Single Institution Experience

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Abstract

Background: In the face of antibiotics resistance and adverse effects, emerging evidence suggests that procalcitonin guided therapy can help enhance appropriate use of antibiotics especially in patients with respiratory infections and sepsis. We seek to assess the uptake of procalcitonin among clinicians in a US hospital and assess its correlation with amount and duration of antibiotics use. We also seek to identify factors significantly associated with antibiotic use. **Methodology:** Retrospective cross-sectional study of patients with sepsis and COPD at a Medical Center in Texas USA. A total 48 COPD and 62 Sepsis patients were assessed. We collected demographic data such as age, weight, height, gender, and race/ethnicity. We also collected data on procalcitonin, number of antibiotics used, duration of antibiotics, and WBC levels at admission. We conducted bivariate analyses and logistic regression analyses to assess factor associated with procalcitonin, number of antibiotics used and duration of antibiotics. **Results:** We had 48 COPD patients and 62 sepsis patients in this study. Overall physicians ordered Procalcitonin on only 11.8% of patients. Procalcitonin was not significantly associated with antibiotics use. However, patients who had procalcitonin ordered had significantly lower WBC count than those without procalcitonin (10.1 vs. 12.9, $p=0.026$). Number of antibiotics was significantly associated with type of diagnosis (Sepsis 66.7% vs. COPD 50.7%, $p=0.001$). In the logistic regression analysis, after adjusting for other variables patients with sepsis were significantly more likely to be on higher number antibiotics (OR 6.08, $p<0.001$) and longer duration of antibiotics (OR 7.44, $p<0.001$). **Conclusion:** Inappropriate use of antibiotics is a public health problem. Procalcitonin has been touted as a biomarker that is effective in reducing use of antibiotics. Our study showed a low utilization of Procalcitonin by physicians and that patients with lower WBC counts were more likely to have procalcitonin ordered. However, our study did not find any association between procalcitonin and the number and duration of antibiotics use.

Introduction

Since the discovery of penicillin by Flemming, antibiotics have played an important role in improving public health in the 20th century^[1]. The last decades of the 20th century saw the proliferation of various antibiotics targeted against various bacterial organisms. However, in the last two decades we have seen the emergence of antibiotics resistance^[1-3]. Antibiotics resistance has both mortality and economic implications in health care. The European Union (EU) estimates that 25,000 patients die yearly from infections from drug resistant bacteria and this is costing the EU about EUR1.5 billion of extra healthcare costs^[4]. In the United States (US), the Center for Disease Control (CDC) estimates that antibiotics resistance contributes to more than two million infections and 23,000 deaths. In terms of health care costs, antibiotics resistance costs the US society about \$2.9M every

year^[5,6]. The cost of antibiotics resistance also extends to lost productivity, prolonged morbidity and other social effects^[5,6].

The key driver of antimicrobial resistance is the selection pressure caused by antibiotic overuse^[2]. Physicians often succumb to the pressure of the immediate needs of the patient at point of care leading to over-prescription of antibiotics^[2,7,8]. Respiratory infections is the third leading cause of disease burden worldwide and is among the most common reasons for antibiotics prescription^[9,10]. However, most of respiratory infections are of viral etiology and its sometimes difficult to clinically differentiate viral and bacterial causes. Several studies have shown that prescription of antibiotics for respiratory infections are often unnecessary or downright inappropriate. Even when necessary antibiotics treatments often exceed recommended duration^[11,12].

Inappropriate antibiotics prescription can lead to several effects – increased cost of care, increased risk of resistance (and its associated costs), increased risk of adverse effects (notably

clostridium difficile infections) and prolonged exposure [3,13]. In view of these unwanted effects, several health care organizations and agencies including the CDC are pushing for responsible use of antibiotics – often described as antibiotics stewardship.

Physicians often rely on clinical judgment when making decisions on starting antibiotics therapy, and other adjuncts such as blood culture are not readily available [14]. Using biomarkers can be helpful in such circumstance. However, conventional biomarkers like complete blood count (CBC) and c-reactive protein (CRP) have their limitations as they are less sensitive and specific in detecting bacterial infections compared to procalcitonin [15,16]. Emerging evidence supports the use of procalcitonin to enhance the diagnosis of bacterial infections and thus improve antibiotics stewardship.

In inflammatory states, procalcitonin is released from many tissues leading to high levels in blood. Potent inducers of procalcitonin release include bacterial endotoxins (lipopolysaccharides), interleukin 6 (IL-6), IF-alpha and TNF-alpha [17,18]. Such increases are rarely seen with viral infections. It's been suggested that viruses release some cytokines that inhibit TNF-alpha and IF-alpha [19-22]. The promise of procalcitonin is in its rapid rise in states of inflammation. It rises within 2-6 hours of inflammation which is faster than the release of CRP [23]. Procalcitonin has been compared to other markers like IL-6, white blood cell (WBC) and CRP and found to be a better discriminant factor in predicting septicemia, respiratory infections, and bacterial infections compared to the others [15,24,25].

Several studies have shown the benefit of procalcitonin guided therapy in reducing the duration of antibiotic use and antibiotics associated side effects without increasing the risk for mortality, recurrent infections, or treatment failures [26-31]. Procalcitonin guided therapy significantly reduced length of hospital stay and reduced the cost of pharmacy care and reduced the length of antibiotics exposure [32]. Contrary to majority of studies, a few studies did not show a difference in antibiotics use in procalcitonin guided therapy which could be as a result of differences in case mix, design, and setting [33]. In view of the campaign for proper antibiotic use, use of procalcitonin can help physicians in making antibiotic decisions in situations of diagnostic ambiguity. However, the uptake of procalcitonin by physicians when making antibiotics prescription decision is unclear. We seek to assess the uptake of procalcitonin among clinicians in a US hospital and assess its correlation with amount and duration of antibiotics use. We also seek to identify factors significantly associated with antibiotic use.

Methodology

This is a retrospective study of patients admitted to a university affiliated community hospital in Texas United States between May 1, 2018 and October 30, 2018. The Medical Center is a 425-bed major referral center for specialized care serving more than a population of 200,000 in East Texas, United States. Participants include adults greater than 18 years who were seen at the medical center during the time frame above.

Data collection

For data collection we engaged the services of hospital transcriptions specialists, who extracted relevant data from the electronic medical records and stored initially in excel file. Relevant data initially extracted include age, gender, ethnicity/race, diagnosis, and dates of admission. We then created a template for further data extraction. With the help of resident physicians, we

further collected clinical data on each of the patients including antibiotics administered, duration of antibiotics, number of antibiotics, white blood count, hemoglobin, platelet count, creatinine, and procalcitonin orders. The data was subsequently de-identified and serial numbers assigned for the purpose of analyses.

Statistical Analyses

We first computed descriptive analysis on all variables collected including frequencies, means and standard deviation. We further did bivariate analysis comparing number of antibiotics administered and duration of antibiotics with procalcitonin orders, creatinine, age, diagnosis, and WBC. Significance testing was done using chi-squared test of proportions and independent t-test of means.

Finally, logistic regression analyses were done using number of antibiotics administered and duration of antibiotics as dependent variables. All other variables were included as independent variables. To facilitate the analyses, the dependent variables were each dichotomized. All analyses were done using the SPSS statistical package version 25.

Results

A total of 540 patients that met the diagnostic code for sepsis and 94 patients with diagnostic code for chronic obstructive pulmonary disease (COPD) exacerbation were initially extracted by the hospital transcription specialist. From these a random sample of 62 sepsis patients and 48 COPD exacerbation patients were selected for extraction of more data. Thus, we had a total of 110 patients for analyses.

Descriptive analysis of the total patient population is presented in Table 1 below. The table shows that the average age of patients in our sample was 65 years. And when we dichotomized by age, 50.9% were 65 years and above. Our sample population was equally distributed gender wise; however, 79.1% were Caucasians. With an average sample weight of 85.57 kilograms and average height of 66.84 inches, the average body mass index (BMI) of the population was 29.7. Per interested variables, only 11.1% (N=13) of the sample had procalcitonin levels ordered.

Table 2 show the result of bivariate analysis between procalcitonin and other variables. There was no significant relationship between procalcitonin being ordered and each of the following variables: number of antibiotics, duration of antibiotics and type of diagnosis. However, patients who had procalcitonin ordered on them had significantly lower WBC count at admission compared to those without procalcitonin (10.1 vs. 12.9, p:0.026).

Table 1: Patient Characteristics

Variable	Mean/%
Age	65.53
Age (dichotomized)	
<= 64	49.10%
>= 65	50.90%
Gender	
Male	50.90%
Female	49.10%
Race	
Black	20.90%
Caucasian	79.10%
Weight (kilograms)	85.57
Height (Inches)	66.84
Basic Labs	
WBC	12.69

HGB	12.48
PLTS	244.27
Creatinine	1.21
Procalcitonin	
Yes	11.80%
No	88.20%
Number of Antibiotics	2.33
Number of Antibiotics	
<= 2	60%
>= 3	40%
Duration of Antibiotics (Days)	4.13
Duration of Antibiotics (Days)	
<= 3	58.20%
>= 4	41.80%
Diagnosis	
Sepsis	43.60%
COPD (Exacerbation)	56.40%

Table 2: Bivariate Analysis on Procalcitonin

	Procalcitonin Ordered		
	Yes	No	P-value
WBC	10.1	12.9	0.026
Number of Antibiotics			0.278
<= 2	9.10%	90.90%	
>= 3	15.90%	84.10%	
Duration of Antibiotics (Days)			0.794
<= 3	12.50%	87.50%	
>= 4	10.90%	89.10%	
Diagnosis			0.689
Sepsis	10.40%	89.60%	
COPD (Exacerbation)	12.90%	87.10%	

Table 3 shows result of bivariate analysis on number of antibiotics. Here again procalcitonin was not significantly associated with number of antibiotics used. However, patients with three or more antibiotics had significantly higher mean creatinine level compared to patients with two or less antibiotics prescribed. Additionally, Table 3 reveals that sepsis patients were more likely to be on greater number of antibiotics compared to patients with COPD exacerbation (66% vs. 50%, p < 0.001).

Table 3: Bivariate Analysis on Number of Antibiotics Used

	Number of Antibiotics		
	<= 2	>= 3	P-value
WBC	11.5	14.2	0.055
Creatinine (mg/dl)	1.01	1.51	0.027
Age	64.3	67.1	0.207
Hemoglobin (g/dl)	12.6	12.3	0.565
Procalcitonin checked			0.278
Yes	46.20%	53.80%	
No	61.90%	38.10%	
Duration of Antibiotics (Days)			<0.001
<= 3	78.10%	21.90%	
>= 4	34.80%	65.20%	
Diagnosis			<0.001
Sepsis	33.30%	66.70%	
COPD (Exacerbation)	50.00%	50.00%	

Table 4 below shows the results of bivariate analyses on duration of antibiotics use. Here again diagnosis was significantly associated with duration of antibiotics. Patients with sepsis were more likely to be on antibiotics for a longer duration compared to

patients with COPD exacerbation (66.7% vs. 22.6%, p < 0.001). Procalcitonin did not show any significant association with duration of antibiotics.

Table 4: Bivariate Analysis on Duration of Antibiotics

	Duration of Antibiotics (days)		
	<= 3	>= 4	P-value
WBC	12.3	12.9	0.64
Creatinine (mg/dl)	1.05	1.25	0.113
Age	65	66	0.597
Hemoglobin (g/dl)	12.65	12.25	0.433
Procalcitonin ordered			0.747
YES	61.50%	38.50%	
NO	57.70%	42.30%	
Number of Antibiotics			<0.001
<= 2	75.80%	24.20%	
>= 3	31.80%	68.20%	
Diagnosis			<0.001
Sepsis	33.30%	66.70%	
COPD (Exacerbation)	77.40%	22.60%	

Tables 5 and 6 show results of logistic regression analyses with number and duration of antibiotics as dependent variables respectively. For both models, after adjusting for age, creatinine level, WBC count and procalcitonin, patients with sepsis were significantly more likely to be on higher number (OR 6.08, p < 0.001) and duration (OR 7.44, p < 0.001) of antibiotics. Procalcitonin was not significantly associated with any of these outcomes.

Table 5: Logistic Regression Analysis Predicting Likelihood of Using >=3 Antibiotics

Variable	OR	Lower CI	Upper CI	P-value
Age	1.02	0.98	1.06	0.403
Creatinine	1.72	0.74	3.99	0.205
WBC	1.04	0.97	1.12	0.243
Procalcitonin (YES)	4.03	1.00	16.24	0.050
Diagnosis (SEPSIS)	6.08	2.32	15.91	0.000

Table 6: Logistic Regression Analysis Predicting Likelihood of >=4 days of Antibiotics

Variable	OR	Lower CI	Upper CI	P-value
Age	1.00	0.96	1.03	0.865
Creatinine	1.07	0.50	2.31	0.854
WBC	0.97	0.91	1.04	0.365
Procalcitonin (YES)	0.88	0.22	3.49	0.857
Diagnosis (SEPSIS)	7.44	2.84	19.51	0.000

Discussion

In our study, we assessed the uptake of procalcitonin by physicians in the management of sepsis and COPD exacerbation. Of the 110 patients assessed, only 11.8% (N=13) of the patients had procalcitonin ordered on their admission. The results reveal a low physicians' uptake of procalcitonin as a tool for managing sepsis and COPD in the hospital setting. Not much studies have been done to assess the use of procalcitonin in managing sepsis and COPD patients. The low physicians' uptake of procalcitonin test in this study may be because procalcitonin test was introduced in the hospital less than six months prior to this study and studies have

shown that adoption of new innovations could be slow in all industries including health care [34].

We also assessed the relationship between procalcitonin and antibiotics prescription viz number of antibiotics and duration of antibiotics. In both the chi squared analysis and logistic regression analyses ordering a procalcitonin test was not associated with number of antibiotics used, duration of antibiotic use and type of diagnosis (SEPSIS or COPD). This finding differs from some studies that showed that procalcitonin reduced the number and duration of antibiotics use [26-32]. However, similar to our finding, a few studies did not show a difference in antibiotics use in procalcitonin guided therapy [33].

Furthermore, our analyses show that patients with lower WBC counts were more likely to have procalcitonin ordered. The mean WBC in those that procalcitonin was ordered was 10 compared with 13 ($p=0.02$) in those it was not ordered (Table 2). This suggests that clinicians are more likely to order procalcitonin when they have in doubt about whether there is an infection such as in patients with lower WBC and probably more likely to start antibiotics without ordering procalcitonin when they have a strong suspicion of an infection e.g. higher WBC. This agrees with previous studies that have shown higher odds of antibiotics prescription when clinicians have a high clinical suspicion of infection [14].

Beyond procalcitonin, our study found that prescription behavior (number of antibiotics and duration of antibiotics) were significantly associated with type of diagnosis. This may not be surprising as physicians are likely to start antibiotics with high WBC and when any patient meets sepsis criteria. In our study, patients with sepsis were significantly more likely to be on higher number (OR 6.08, $p < 0.001$) and duration (OR 7.44, $p < 0.001$) of antibiotics.

There are some limitations in our study. First our study had a small sample size which could have affected the ability to detect a difference between the procalcitonin and non-procalcitonin groups. Although we did not perform a rigorous sensitivity analyses, an anecdotal comparison of our sample size with other studies suggests our small numbers could have underpowered our study to detect a significant difference. Secondly, our study had a retrospective and cross-sectional design; thus, it is more prone to threats to internal validity compared to prospective randomized controlled trials.

Conclusion

Inappropriate use of antibiotics is a public health problem. Procalcitonin has been touted as a biomarker that is effective in reducing use of antibiotics. Our study showed a low utilization of procalcitonin by physicians and that patients with lower WBC counts were more likely to have procalcitonin ordered. However, our study did not find any association between procalcitonin and the number and duration of antibiotics use.

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